Remarks

Claims 1 and 4-24 are pending in the subject application. By this Amendment, Applicants have amended claims 1, 21, 23, and 24. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1 and 4-24 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 1 and 4-24 are rejected under 35 USC §103(a) as obvious over Sierra *et al.* (U.S. Patent No. 5,290,552) in view of Matsueda *et al.* (U.S. Patent No. 4,927,916) and Bhargava *et al.* (1989) and further in view of Good (U.S. Patent No. 5,342,283). The Examiner asserts that at the time of the subject invention a person of ordinary skill in the art would have been motivated to combine a composition as taught in the Sierra *et al.* patent as a delivery vehicle for a radiotherapeutic agent as taught by the Matsueda *et al.* patent or the Bhargava *et al.* reference. The Good patent is cited as teaching that the use of various radionuclides based upon the properties thereof (*e.g.*, half-life) is well known in the art. Applicants respectfully traverse this ground of rejection.

Applicants respectfully assert that the cited references, whether taken alone or in combination, do not teach or suggest the claimed invention, or the advantages of the invention over the teachings of the cited art. The Examiner has indicated in the outstanding Office Action that the claimed compositions simply form an alternative method of controlled release, and that the therapeutic agents immobilized in the compositions of the invention will eventually be released. However, even if the agents are eventually released due to, for example, degradation of the glue, this will not occur until after the therapeutic agents have exerted a localized therapeutic effect around the area of the tissue glue. The claimed compositions are, therefore, characterized by the ability of the agent to mediate localized therapeutic activity when the agent is immobilized in the tissue glue. The compositions have a radiotherapeutic effect locally, in the immediate vicinity of their site of application, during the time when the agent is immobilized in the glue. The extent of the therapeutic effect is localized due to the immobilization of the agent at the desired location. This allows the specific localized delivery of radiotherapeutics to the required site of action in, for example, brachytherapy. The ability of the agents to exert a therapeutic effect while the agents are

immobilized means that the radiotherapy can be accurately targeted to the required location, and acts to minimize the exposure of neighboring tissues to the radiotherapeutic effect.

In contrast, the compositions taught in the cited references are designed specifically to delay or prolong the release of the therapeutic agents and thereby delay the agent's therapeutic activity. The agents themselves will have no therapeutic effect until they are actually released from the tissue glue. In effect, the tissue glue simply acts to "store" the agents in an appropriate location until the agent is released. The cited documents all require that, for therapy to occur, the agent must actually leave the tissue glue. As already noted by Applicants, the compositions of the subject invention provide for localized radiotherapeutic effects while immobilized in the tissue glue. Thus, the cited references relate to compositions which contain a different type of therapeutic agent from that of the claimed invention and which operate in a different way from that of the claimed invention. Applicants respectfully assert that the compositions described in the references cited by the Examiner are not capable of exerting a therapeutic effect when immobilized in a tissue glue as required by the claimed invention.

While the Sierra *et al.* patent may describe a surgical adhesive which may additionally comprise therapeutically active substances, in particular growth factors, cytokines or immunoglobulins (column 4, lines 63-66, to column 5, lines 7-12), it is clear that such therapeutically active substances would need to be released from the adhesive material in order to have any therapeutic effect. In attempting to rebut Applicants' arguments in their Amendment dated March 24, 2003 that the Sierra *et al.* patent requires that the therapeutically active substance must be released from the adhesive material, the Examiner refers to the list of substances at column 5, lines 14-15, of the Sierra *et al.* patent as examples of substances which do not have to be released from the adhesive material. However, none of these substances are therapeutically active. These substances are all components which may be added to the adhesive to alter the properties of the adhesive itself, *i.e.*, to achieve the "physical" advantages mentioned at column 4, line 65, of the Sierra *et al.* patent. The Sierra *et al.* patent lists the components as "structural materials." Such components are unrelated to any therapeutic effect that may be achieved by the adhesive composition and would not be considered by a skilled person seeking to achieve such a therapeutic effect.

Thus, Applicants maintain that the only therapeutic agents described in the Sierra *et al.* patent are those which must be released from the adhesive in order to reach their sites of action in the surrounding tissue and thereby achieve a therapeutic effect. The adhesive material of Sierra *et al.* therefore functions simply to store these substances and thereby to delay or prolong their delivery or release into the surrounding tissue. There is no suggestion in Sierra *et al.* that such compositions described in the Sierra *et al.* patent could have any therapeutic activity before release of the substances from the adhesive. Moreover, there is no suggestion that the adhesive compositions could comprise any therapeutic agent which is capable of exerting localized therapeutic activity while immobilized in the adhesive. In particular, there is no suggestion of using any kind of radiotherapeutic agent in combination with the adhesive of Sierra *et al.*, and the agents referred to in Sierra *et al.* are of a wholly different type and purpose to those of the present invention. Indeed, the purpose of including therapeutic agents in the adhesive of Sierra *et al.* is to achieve a controlled release of the agents. Any therapeutic effect achieved while the substance is immobilized, rather than just on release from the adhesive, would be contrary to the purpose of such a controlled release vehicle. Therefore, the Sierra *et al.* patent teaches the ordinarily skilled artisan away from the present invention.

The Matsueda *et al.* and Bhargava *et al.* references both describe radiolabeled antibodies. These documents teach the use of radionuclides for labeling antibodies. Although the Bhargava *et al.* reference does mention that radiolabeled antibodies may be used for therapeutic purposes, the focus of the reference is clearly on methods for radiolabeling antibodies, and not on the use of radiolabeled antibodies for therapy. It is clear from the disclosure of the cited references that the antibodies described in the Matsueda *et al.* and Bhargava *et al.* references must be released into the body in order to bind their targets and have a therapeutic effect. There is no teaching or suggestion in either reference that the antibodies exert any kind of therapeutic effect while they are immobilized at a distance from their target site. Rather, both the Matsueda *et al.* and Bhargava *et al.* references require that the antibodies are free to bind to the specific target site and, thus, could not be effective while immobilized in a tissue glue.

Applicants respectfully maintain that the ordinarily skilled artisan, at the time of the present invention, had no incentive to combine the teachings of Sierra *et al.* with that of Matsueda *et al.* or

Bhargava *et al.* The Matsueda *et al.* patent and the Bhargava *et al.* reference provide radiolabeled antibodies that must bind to specific targets in order to have an effect. Such radiolabeled antibodies must therefore be released into the target tissue, and not immobilized in a tissue glue. There would be no motivation for the skilled artisan to include such antibody components in an adhesive material, such as that described in Sierra *et al.*, as this would prevent the antibodies from reaching the target tissue.

The newly cited Good patent describes radioactive implants for use in brachytherapy. These elements are designed to be permanently implanted, or temporarily implanted for subsequent removal, into human tumor tissues (see, for example, column 6, lines 29-30, lines 43-44, and lines 49-51). The ordinarily skilled artisan would not combine the teaching of the Good patent with that of the Sierra *et al.* patent. As noted above, the Good patent describes radioactive implants that are designed to be directly implanted into the body. There would be no motivation for the skilled artisan to look to the Sierra *et al.* patent, which is directed to "tissue glue" type adhesives *per se*, and only briefly mentions the potential for including releasable therapeutic agents in such adhesives. As explained above, the Sierra *et al.* patent teaches the use of adhesives for the controlled release of therapeutic agents, in order to delay or prolong delivery of the agents to an area of tissue. The implants of the Good patent are for direct implantation. Clearly it is a priority in such brachytherapy treatment to restrict the exposure of surrounding tissue to the radiotherapeutic effects of the implants. This is why the implants of the Good patent are specifically designed for permanent implantation or temporary removable implantation. It is important to minimize the spread of any radiotherapeutic agent into tissues other than the target. The teaching of Sierra *et al.*, which describes only compositions for the controlled release of therapeutic agents, would therefore not be applied to the implants disclosed in the Good patent.

Applicants have unexpectedly discovered that it is possible to immobilize a radiotherapeutic agent in a tissue glue for a sufficient time that (a) the immobilized agent can exert a localized radiotherapeutic effect on the adjacent tissue, and (b) the immobilization lasts for a sufficient number of half lives of the radiotherapeutic agent such that the radiotherapeutic activity of the agent is minimal at the point when the agent is released from the tissue glue. The present invention provides the further unexpected advantage over the prior art that radiotherapeutic agents can be used which

will be degraded themselves upon release from the tissue glue. This further reduces the likelihood of effecting neighboring tissues and also obviates the need to remove the agents after the course of therapy has been completed as is required using the implants taught in the Good patent. Thus, Applicants respectfully assert that the compositions disclosed in the cited references contain a different type of therapeutic agent from the subject invention and operate in a different way from the compositions of the subject invention. In a sincere effort to expedite prosecution of the subject application to completion, claims 1, 21, 23, and 24 have been amended to clarify the differences between the invention as claimed and the disclosure of the references cited by the Examiner under this rejection. The claims now specify compositions comprising agents that mediate localized radiotherapeutic activity when immobilized in the tissue glue.

Applicants respectfully assert that the claimed compositions and methods are not obvious over the references cited by the Examiner. The combination of the Sierra *et al.* patent, in view of Matsueda *et al.*, Bhargava *et al.*, and Good references, does not teach or suggest each and every element of the claimed invention and does not provide the ordinarily skilled artisan with any motivation to develop compositions comprising a radiotherapeutic agent that has a radiotherapeutic effect while immobilized in a tissue glue. Such an arrangement is neither taught nor suggested in the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl